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LETTER

Long-term stroke risk in meningioma patients treated with conventionally fractionated photon-based radiation therapy

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Conventionally fractionated radiotherapy (RT) has been a stalwart radiation-based treatment modality for intracranial meningioma for decades, providing excellent tumor control (1). Although the majority of patients receive conventional photon-based therapy, the physical properties of proton beam make this radiation modality very attractive, leading to a dramatic growth in the number of proton centers across the United States (2). The increasing popularity of protons over the past decade may lead to increased proton utilization in the management of benign conditions, where long-term survival is expected, such as meningioma (3). A recent randomized study of RT from the Massachusetts General Hospital involving an 80%/20% proton/photon ratio during treatment for subtotally resected/recurrent benign meningioma patients found the risk of stroke was 20.5%, with the average stroke developing 5.6 years after RT completion (4). This high rate is worrisome and puts the safety of external beam radiation therapy in the management of benign meningioma under question. However, before rejecting radiation therapy as a management for benign meningiomas, it is important to determine whether this high rate of stroke is also evident in patients treated with photon-based conventionally fractionated RT. This study was performed to address this void.

Studies examining RT for meningioma were assessed using an extensive search of the PubMed database. Search terms used were "long-term", "fractionated", "radiotherapy", and "meningioma". To optimize stroke inclusion, only studies with mean/median clinical follow-up of at least six years were included in the final analysis in order to exceed the 5.6 year lag time between completion of RT and stroke development established by Sanford et al. (4). Additional inclusion criteria were: a) minimum of 30 patients, b) English language, c) exclusive RT patient population, d) exclusive meningioma population, e) comprehensive post-RT morbidity analysis, and f) non-duplicant patient pool. Proton therapies were excluded from the analysis. The stroke rate for each article was assessed either from being directly described in the manuscript, or from extrapolating post-RT complications from reported clinical examinations (i.e. hemiparesis/weakness, pituitary dysfunction following treatment of cavernous sinus lesions given the known course of the internal carotid

artery in that anatomic region) at last follow-up in order to rule out transient events. Results were then culled to determine an overall stroke rate. Six studies examining RT for meningioma with long-term follow-up met inclusion criteria, providing a total of 303 patients as shown in Table 1 (5-10). Median/mean follow-up ranged from 78 to 168 months. Operative meningioma resection prior to fractionated RT occurred in 213 patients (70.3%). Mean total dose ranged from 45.1 Gy to 57.6 Gy; the mean dose per fraction ranged from 1.7 to 2.0 Gy (Table 1). Seventeen patients suffered a stroke following RT, for a stroke rate of 5.6% (Table 1); the vast majority of these strokes were deduced from reported clinical manifestations, most predominantly hemiparesis either caused or worsened by RT. All six studies used exclusively photons for RT.

The results of our PubMed database search show a dramatically lower long-term stroke rate at 5.6% with photon-based therapy. This rate is in line with the normal expected rate of stroke for people ages 40-79 according to the American Heart Association (11). Therefore, it is possible that the high stroke rate seen in the randomized clinical trial may be related to the use of proton beam; another possibility, independent of technique, is the dose prescription in both arms of that study. Additionally, the Bragg peak phenomenon may have resulted in a higher radiobiological effect upon adjacent cerebral vessels thereby resulting in vascular damage. The retrospective nature of this study and inability to determine the individual dosing, follow-up, treatment plans, and detailed clinical course (symptom onset, intervention, imaging findings, etc.) of the 17 patients who suffered post-photon RT stroke are limitations of this study. Another limitation is that the deductive approach used for identifying stroke could potentially overestimate or underestimate the true incidence of stroke following RT. Nevertheless, this information suggests that additional studies are greatly needed to determine the most effective and safe method of treating patients with benign meningiomas.

In conclusion, the long-term stroke risk of RT using photons is 5.6%, in line with the expected rate of stroke development in a general population. Given that the results of Sanford et al. are based on an 80% proton-based therapy, it is pertinent to wonder whether the long-term stroke morbidity of 100% proton-based RT may be higher than their 20.5% rate. Further studies with sufficient follow-up will be required to definitively address this issue.

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Table 1. Studies meeting inclusion criteria (minimum clinical follow-up = 72 months) for long-term stroke evaluation following fractionated radiotherapy (RT) for meningioma

Reference	No. patients	Follow-up (months)	Resection prior to RT	RT as primary treatment	Clinical evidence of stroke	Stroke incidence (%)	Mean dose (Gy)	Mean dose per fraction (Gy)	RT modality
5	61[a]	108 (median)	61	0	7	11.5	57.5	1.7	Photon
6	49	168 (median)	34	15	3	6.1	45.1	2.0	Photon
7	45	108 (mean)	45	0	7	15.6	52.0	1.8	Photon
8	38	89 (median)	20	18	0	0	53.0	1.9	Photon
9	57	78 (median)	28	29	0	0	57.6	1.8	Photon
10	53	83 (median)	25	28	0	0	52.9	1.9	Photon
Total	303		213	90	17	5.6			

[a]Assessable for late toxicity (of the 82 patients total in this study).

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